HHS Public Access

Author manuscript

Neuropsychol Rehabil. Author manuscript; available in PMC 2021 October 06.

Published in final edited form as:

Neuropsychol Rehabil. 2020 October ; 30(9): 1666–1681. doi:10.1080/09602011.2019.1598876.

Neurocognitive Functioning in Symptomatic Adults with Sickle Cell Disease: A Description and Comparison with Unaffected Siblings

Staci Martin[1], **Marie Claire Roderick**[1], **Cristina Abel**[1], **Pamela Wolters**[1], **Mary Anne Tamula**[2], **Courtney Fitzhugh**[3,4], **Matthew Hsieh**[3], **John Tisdale**[3]

[1]Pediatric Oncology Branch, National Cancer Institute, 9030 Old Georgetown Road, Bldg 82, Bethesda, MD, USA

[2]Clinical Research Directorate/Clinical Monitoring Research Program, Leidos Biomedical Research Inc., NCI Campus at Frederick, Frederick, MD 21702

[3]Molecular and Clinical Hematology Branch, National Heart Lung and Blood Institute, 9000 Rockville Pike, Bldg 10, Bethesda, MD 20892, USA

[4]Hematology Branch, National Heart Lung and Blood Institute, 9000 Rockville Pike, Bldg 10, Bethesda, MD 20892, USA

Abstract

Children and adults with sickle cell disease (SCD) are at risk for neuropsychological deficits; however, the neurocognitive functioning of adults with SCD and related comorbidities has not been widely reported in the literature. We examined specific cognitive domains in symptomatic adults with SCD and compared them with their unaffected siblings. We also examined relationships between cognitive scores, patient-reported outcomes (PROs), and medical/laboratory values. Thirty patient-sibling pairs (*M* patient age = 32.5 years, *M* sibling age = 32.1 years) completed evaluations as part of a medical clinical trial (NCT00061568). All patient and sibling neurocognitive test scores were within normal limits. Patients scored significantly lower (M=91.0±11.3) than their siblings (M=100.6±12.3; t=−3.5, p<.01) on the Wechsler Processing Speed Index. They also indicated more problems than siblings on an executive functioning questionnaire, although these differences were nonsignificant after accounting for depressive symptoms. Higher fetal hemoglobin and lower creatinine correlated with better scores on particular cognitive and PRO measures. In summary, our sample of adults with symptomatic SCD demonstrated worse processing speed and experience more executive challenges than their siblings, despite treatment with hydroxyurea. These relative weakness likely relate to disease processes but the specific physiological mechanism is unclear.

Correspondence: Staci Martin, Pediatric Oncology Branch, National Cancer Institute, 9030 Old Georgetown Road, Bldg 82, Bethesda, MD, USA, martins@mail.nih.gov.

Disclosure of conflicts of interest

The authors declare no conflicts of interest.

Keywords

Sickle Cell Disease; Neurocognitive Functioning; Processing Speed; Sibling Controls; Sickle Cell Trait

Individuals with sickle cell disease (SCD) are at risk for neuropsychological deficits, often related to the occurrence of ischemic injury (Kral, Brown, & Hynd, 2001; Strouse, 2016). Impairments in global cognitive functioning have been found among children with overt cerebrovascular accidents as well as those with silent infarcts (Gold, Johnson, Treadwell, Hans, & Vichinsky, 2008; Nunes, Argollo, Mota, Vieira, & Sena, 2017; Schatz, Finke, Kellett, & Kramer, 2002). Some evidence suggests that even children with SCD with no known history of infarcts (i.e., no visible brain abnormalities on MRI scans) perform worse on cognitive measures compared to healthy children (Schatz et al., 2002; Steen et al., 2005). In addition, hemoglobin oxygen saturation levels (King et al., 2014) and hematocrit (Steen et al., 2003) are among the biological factors linked to global cognitive scores in children with SCD. Importantly, measures of specific abilities, such as attention and processing speed, are likely more informative about cognitive functions in SCD than global IQ scores (Brown et al., 2000; Schatz et al., 2002) since they appear more sensitive to the effects of CNS pathology that may be present.

The long-term consequences of such deficits in childhood are likely to impact adult functioning, although neurocognitive outcomes in adults with SCD have not been widely reported in the literature to date. In one published study on this topic, Mackin and colleagues with the Neuropsychological Dysfunction and Neuroimaging Adult Sickle Cell Anemia Study Group reported lower functioning in adults with neurologically asymptomatic sickle cell anemia (SCA) compared with healthy control participants (2014). Decrements were in domains of visual-spatial skills, processing speed, and working memory, and were associated with structural changes in the brain, including reduced volume in the basal ganglia and thalamus. These types of neurocognitive deficits can lead to poorer quality of life (Sanger et al., 2016), as evidenced by individuals with SCD having lower educational and financial attainment as well as a higher likelihood of unemployment compared to individuals without SCD (Laurence, George, & Woods, 2006).

One other published study by the aforementioned group comprehensively investigated the neurocognitive functioning of neurologically asymptomatic adults with SCA. Vichinsky et al compared the functioning of 149 asymptomatic adults with SCA to a sample of healthy unrelated controls using a comprehensive IQ test and several other neurocognitive measures (2010). Exclusion criteria included a history of stroke or other abnormal neurological impairment, depression, and chronic disorders such as hypertension, liver, lung, or renal disease. Results revealed that the adults with SCA performed significantly lower than the control participants in various domains, including nonverbal reasoning, working memory, executive functioning and processing speed. Scores were generally at the low end of average or just slightly below the Average range. Neuroimaging variables did not account for the differences between the groups.

While the study by Vichinsky and colleagues (2010) provides a comprehensive picture of neurocognitive functioning among asymptomatic adults with SCA, no published studies to our knowledge have focused on the functioning of symptomatic adults with SCD. Given the cognitive deficits and the prevalence of significant health problems seen in this population, further research is needed to understand the neurocognitive functioning of SCD patients who are actively symptomatic. Our primary aims were to examine specific cognitive domains in symptomatic adults with SCD, and to compare the cognitive functioning of these patients with their unaffected siblings. Based on the results of the Mackin et al. (2014) and Vichinsky et al. (2010) studies, we hypothesized that patients would score lower than their unaffected siblings on measures of nonverbal reasoning, processing speed, working memory, and executive functioning. A secondary aim was to examine relationships between cognitive scores, medical diagnoses, and laboratory values.

Methods

Eligibility criteria

All patients ages 18 and older who enrolled on a larger medical protocol (described below) were eligible to participate in this neuropsychological substudy. To meet criteria for the medical protocol, patients had to be at high risk for disease-related morbidity or mortality, defined by the presence of irreversible organ damage (e.g., stroke, renal insufficiency, vaso-occlusive crises, etc.) or potentially reversible complications not ameliorated by hydroxyurea. Psychotic symptoms, extreme behavioral difficulties, and/or severe cognitive impairment (i.e., IQ estimated to be below 70) were exclusion criteria for this substudy.

Participants

Participants included individuals with sickle cell anemia who had a human leukocyte antigen-matched family member and were prospectively enrolled on a transplant protocol at the National Heart, Lung, and Blood Institute at the National Institutes of Health. Patients on the medical protocol were scheduled to receive a stem cell transplant from their sibling donor. Neurocognitive testing was completed prior to patients starting the pre-transplant conditioning regimen and prior to siblings donating their cells. No patients declined to participate in this neuropsychological substudy. All sibling donors agreed to participate, except for one individual who did not want to complete the assessment due to time constraints; data from this patient-donor pair were not included in the current analyses. No potential patients or siblings met exclusion criteria.

Measures

Nonverbal Skills—The Performance IQ (PIQ) of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) was administered as a brief measure of nonverbal abilities. The WASI PIQ is comprised of two subtests: Block Design and Matrix Reasoning. The PIQ composite score was examined in this study. Wechsler IQ scores are compared to a mean of 100 and standard deviation of 15.

Processing speed—The Processing Speed subtests of the Wechsler Adult Intelligence Scale – Fourth Edition (WAIS-IV; Wechsler, 2008) were administered to assess speed of

mental processing. The Coding and Symbol Search subtests both are timed, pencil and paper measures; the scaled scores are combined to yield a composite Processing Speed Index (PSI) that was included in analyses for this study (mean = 100, SD = 15).

Working memory—Digit Span is a multi-part subtest of the WAIS-IV. On the Digits Backward task examined for this study, participants are asked to repeat increasingly long sequences of numbers in reverse order as a measure of working memory. Scaled scores are obtained and compared to a mean of 10 and standard deviation of 3.

Executive functioning—The Trailmaking subtest from the Delis-Kaplan Executive Function System (DKEFS; Delis, Kaplan, & Kramer, 2001) was administered to assess executive skills. The score on the Number Letter Switching task was analyzed for this study. This score represents cognitive flexibility, or one's ability to shift between mental sets, which is a core component of executive functioning. Validity of the DKEFS is well-established (Jefferson, Poppas, Paul, & Cohen, 2007).

Patient reported outcomes (PROs)—A PRO measuring executive skills in the home environment, the Behavior Rating Inventory of Executive Function – Adult (BRIEF-A), was administered (Roth, Isquith, & Gioia, 2005). On this 86-item questionnaire, examinees rate how true the statements are (Never, Sometimes, Almost Always) in the past six months. Raw scores are converted to T-scores (mean = 50, SD = 10). Responses yield T-scores on nine subscales (Inhibit, Shift, Emotional Control, Self-Monitor, Initiate, Working Memory, Plan/Organize, Task Monitor, and Organization of Materials) and three global indices (Behavioral Regulation Index, Metacognition Index, and Global Executive Composite). The BRIEF-A has been validated in numerous populations, including adults with chronic illness (Baker, Gibson, Georgiou-Karistianis, Roth, & Giummarra, 2016; Pham et al., 2015).

The Brief Symptom Inventory-18 (BSI-18; Derogatis, 2000) is an 18-item PRO measuring somatization, depression and anxiety. While emotional functioning is not a focus of this study, the BSI-18 Somatization and Depression subscales were covaried in analyses of patient-sibling differences. Raw scores for this measure are converted to T-scores based on community norms. Use of the BSI-18 has been supported across multiple populations and ethnicities (Petkus et al., 2010; Wiesner et al., 2010).

The McGill Pain Visual Analogue Scale (VAS) item of the Short-Form McGill Pain Questionnaire (Melzack, 1987) is a PRO assessing pain intensity. The VAS is a horizontal line (100 mm) anchored by two descriptors for each extreme (e.g., no pain, worst possible pain). Respondents rate their pain intensity within the past week by marking a slash on the line, and their score is the number of mm between 0 and their mark. Higher scores represent more severe pain. The McGill Pain VAS is widely used and is considered a reliable and valid measure of pain (Chapman et al., 2011; Scrimshaw & Maher, 2001).

Medical and laboratory values—We documented medical complications that may relate to cognitive outcomes, including history of stroke (overt and silent) and transient ischemic attack (TIA). A history of other sickle cell-related complications was also noted for descriptive purposes. Obtained laboratory values included in analyses were hemoglobin and

fetal hemoglobin, alkaline phosphatase, and creatinine. We report on additional laboratory values descriptively, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactic acid dehydrogenase (LDH).

Procedures

Approval was obtained for the larger medical study, which included this neurocognitive substudy, from the Institutional Review Board of the National Heart, Lung, and Blood Institute (NCT00061568). Patients came to the NIH for this transplant study from all over the United States as well as from several African countries. Neurocognitive assessments for the patients and siblings typically lasted about 3 hours. Individuals were not tested when they were febrile. Breaks were given as needed.

Medical and laboratory data were obtained through electronic medical record review. Laboratory values were taken from the date closest to the neuropsychological evaluation; this was often on the same day and no more than one week out from testing.

Statistical analysis

To examine the primary objective of assessing specific neurocognitive domains among symptomatic adults with SCA, we calculated descriptive statistics on cognitive and medical variables. Variables that were not normally distributed (i.e., Performance IQ, Digits Backward, Trails Switching, and all laboratory values except hemoglobin) were subjected to a log transformation. Paired t-tests were computed to compare mean scores between patients and siblings on laboratory values as well as cognitive and PRO variables. For significant patient-sibling differences in cognitive scores, an analysis of covariance (ANCOVA) was conducted to control for the effects of somatic symptoms, using BSI Somatization subscale scores. Given results of correlational analyses, two ANCOVAs were conducted to examine patient-sibling differences on the BRIEF-A composite scores (Behavioral Regulation Index and Metacognitive Index) while holding constant the effects of depressive symptoms using the BSI Depression subscale scores. (Only these two composite scores, rather than all of the subscales, were examined in order to reduce experimentwise error). To assess the relationships between cognitive scores, PRO scores, and laboratory variables among patients only (not siblings), we performed Pearson r correlations while partialing out the variance from years of education. Analyses were conducted using SPSS Statistical Software version 1.0.0.1058.

Results

Demographic variables in patients and siblings

Thirty patient-sibling pairs completed the evaluations for this study. Patients and siblings were similar in terms of age (patient M age = 32.5 ± 7.5 years; sibling M age = 32.1 ± 8.3 years) and years of education (patient M = 15.8 ± 2.4; sibling M = 16.0 ± 2.5; ps > .05). Gender distribution also was comparable across patients and siblings; 23% of patients were male, compared to 27% in the sibling group (X^2 = .6, p > .05). Forty-seven percent of the patients were African (i.e., born and raised in Africa) and 53% were African-American.

Medical variables in patients

As shown in Table 1, most of the patients had a history of one or more sickle cell-related complications. Eight of the 30 patients had a history of either an overt ($n = 2$) and/or silent ($n = 7$) stroke, and one of these eight patients had both an overt and silent stroke. Other diagnoses that were documented somewhat frequently were avascular necrosis (41%) and sickle liver disease (36%). Ninety-three percent had been treated with hydroxyurea. All but one patient (96%) had undergone at least one blood transfusion in the past, and slightly less than half (43%) of the patients had experienced iron overload; 31% had been on chelation therapy. Seventy-seven percent had an active prescription for an opioid medication at the time of the baseline evaluation. Twenty percent had a psychiatric diagnosis (10% depression, 3% anxiety, 7% both depression and anxiety).

Several of the mean lab values of patients were abnormal, as would be expected in SCD. Also as expected, all lab values were significantly different between patients and their siblings, with the exception of ALT (Table 2).

Cognitive test scores of patients and siblings

Cognitive test results for the patients and sibling donors are shown in Table 3. Mean scores on all cognitive measures were in the Average range. Among patients, age was unrelated to any of the cognitive test scores or PRO scores. More years of education were related to higher scores on the DKEFS Trails Switching test ($r = .42$, $p < .05$). Patients who were African-American did not score significantly different than African patients on any of the measures. A comparison of patients with ($n = 8$) versus without ($n = 22$) a history of either an overt or silent stroke revealed no significant differences on any of the cognitive tests or PRO measures (ps > .05).

In comparing the cognitive test scores between patients and their siblings, only one significant difference emerged. Patients scored lower ($M = 91.0$, $SD = 11.3$) than their sibling donors ($M = 100.6$, $SD = 12.3$; $t = -3.5$, $p < .01$) on the Processing Speed Index (PSI). This difference remained significant after controlling for the effects of physical symptoms by covarying out BSI Somatization scores ($F[2,59] = 4.63$, $p < .05$).

Regarding PRO measures, all BRIEF-A scores were within normal limits for both patients and siblings (see Table 4), indicating intact executive functioning. However, patients scored significantly higher than their sibling donors (indicating more symptoms) on subscales assessing their ability to inhibit impulses (Inhibit), initiate new tasks (Initiate), remember newly presented information (Working Memory), plan and organize their thoughts and behaviors (Plan/Organize), organize materials in order to complete a task (Organization of Materials), and regulate their emotions (Emotional Control) (all ps < .05). Patient scores also indicated significantly higher levels of executive dysfunction compared to their siblings on the Behavioral Regulation Index and Metacognition Index composite scores (ps < .05). To examine potential contributions of depressive symptoms, we conducted a MANCOVA on the two BRIEF-A composite scores adjusting for BSI-18 depression scores. Results showed that the differences between patients and siblings on the Metacognitive Index ($F = 3.76$, $p = .057$) and the Behavioral Regulation Index ($F = 3.37$, $p = .07$) were no longer significant. In

general, patients are reporting more perceived problems than their sibling counterparts in a few distinct areas of executive functioning that seem to relate, at least in part, to depressive symptoms.

Relationships between cognitive variables, PRO measures, and pain variables

There were no significant relationships between mean cognitive test scores and pain intensity scores among patients (*p*s > .05). However, higher pain intensity in the past week was related to more problems on the Initiate ($r = .39$, $p < .05$), Plan/Organize ($r = .42$, $p < .05$), and Organization of Materials ($r = .46$, $p < .05$) subscales of the BRIEF-A measure of executive functioning.

Relationship between cognitive test scores, PRO measures, and laboratory variables

For patients only, the relationships between laboratory values and cognitive and PRO scores were examined while covarying years of education (see Table 5). With respect to cognitive test variables, creatinine levels were negatively correlated with DKEFS Trails Switching scores ($r = -.45$, $p < .05$). Regarding the relationships between laboratory values and PRO scores, higher hemoglobin levels were correlated with higher scores (more problems) on the BRIEF Task Monitor subscale ($r = .41$, $p < .05$).

Discussion

To our knowledge, this is the first study to present a comprehensive description of neurocognitive variables among symptomatic adults with SCA. This type of comparison with siblings is important because it allows for better estimation of the disease impact on cognitive functioning, as the siblings essentially act as a control for early environment and genetics. Inclusion of these two features help to fill the literature gap in our understanding of how SCD affects cognitive functioning over the entire clinical spectrum of SCD patients.

While the adults with symptomatic SCD in our sample performed within normal limits and similar to their sibling donors on cognitive tests, they were significantly slower in the processing speed domain. This discrepancy is consistent with prior research (Vichinsky et al., 2010). In line with this, a recent study by Crawford and Jonassaint (2016) found that the differences in cognitive scores between adults with SCD and healthy controls were smaller after adjusting for processing speed. These collective results suggest that having anemia with SCD (with a mean hemoglobin level of 8.2 g/dL in the aforementioned Vichinsky study (2010) and 8.8 g/dL in our study) was the consistent factor across these investigations, and may be a large contributor to patients having slower processing speed.

Our methods differed from Vichinsky et al's study in other respects. Importantly, Vichinsky and colleagues used unrelated but demographically matched community controls and none with sickle trait, whereas we evaluated unaffected siblings as controls and half of them had sickle trait. Our use of a sibling comparison group allows for more exertion of control over factors such as family environment, education, and socioeconomic status (White & DeBaun, 1998). Finally, all patients in our study were either neurologically symptomatic and/or had multiple SCD-related complications (i.e., organ injuries), and several had a positive

psychiatric history. Race was different across studies as well, with almost half of our sample being African; all patients in the Vichinsky study were self-described as African-American.

The study by Vichinsky and colleagues (2010) is well-designed and provides an important, comprehensive picture of asymptomatic SCA, yet their stricter exclusion criteria resulted in a sample that was relatively healthy, neurologically intact, and psychologically stable; as such, their findings may not be widely representative, as suggested by Ballas (2010). However, as mentioned above, mean cognitive scores from our patient sample were comparable or higher, in general, despite our patients being more symptomatic. Reasons for this are unclear, but we speculate that this could relate to our referral pattern of higher functioning in individuals (and families) who come to the NIH for intensive research studies, even though they were physically sicker.

In addition to the difference in processing speed between patients and siblings in our study, more differences were noted on the PRO measure of executive functioning (BRIEF-A). Patients perceived more problems in their ability to initiate tasks, plan and organize their thoughts and materials, employ working memory skills, and regulate their emotions compared to their siblings' perceptions. None of these mean scores were in the clinically significant range, but the fact that they were endorsing significantly more problems than their siblings is noteworthy. It is important to note that the patient-sibling differences on the two BRIEF-A composite scores were no longer significant when considering depressive symptoms. However, given that the p values for these analyses approached significance at the .05 level, it is possible that with a larger sample those differences would have remained significant after covarying depression scores.

More endorsement of executive symptoms was related to recent pain experience; while this relationship in our study is correlational rather than causal, the suggestion that pain may interfere with optimal executive skills is plausible and has been borne out in other studies of clinical and experimentally-induced pain (Berryman et al., 2014; Bjekic, Zivanovic, Puric, Oosterman, & Filipovic, 2017; Murata et al., 2017). Also, these symptoms may interfere with patients' abilities to perform their best at school or work and, as another recent study suggested, this relationship may account for low employment rates in this population (Laurence et al., 2006; Sanger et al., 2016). Given the generally intact cognitive functioning found in our patients and their siblings, perhaps patients have the intellectual potential to succeed in school and at work, but their pain and executive difficulties prevent them from reaching their potential in these realms.

While our use of unaffected siblings as a comparison group allows us to infer that the patients' slower processing is related to disease processes, the specific physiological mechanism is unclear. For example, 27% of our patients had a history of an overt or silent stroke, but surprisingly there were no differences in cognitive test scores or questionnaire variables between those with and without a stroke history. Prior research has put forth evidence of a relationship between cytokine levels and executive function test scores in children with SCD (Andreotti, King, Macy, Compas, & DeBaun, 2015). Moreover, magnetic resonance imaging (MRI) studies have documented negative associations between children's processing speed and the apparent diffusion coefficient (ADC; a measure of white matter

integrity) in the right frontal lobe and cerebellum in SCD (Scantlebury et al., 2011). Little is known about whether these relationships remain significant in adults with SCD, and this is an area for future research to address.

Laboratory values also have been implicated in cognitive processes among individuals with SCD, and results of the current study underscore the importance of these relationships and highlight new ones that warrant further exploration. First, our correlational results suggest that patients with higher fetal hemoglobin process information faster than those with lower fetal hemoglobin. Hydroxyurea may be the largest contributor to this relationship, as it is known to increase the production of fetal hemoglobin, a mechanism that could increase oxygenated blood to the brain (Lanzkron et al., 2008). Previous research has shown that children with SCD treated with hydroxyurea performed better on several cognitive tests than an untreated group, although processing speed was not measured independently (Puffer, Schatz, & Roberts, 2007). Other research has revealed poorer non-verbal reasoning skills among older patients with SCD with low hemoglobin levels (Vichinsky et al., 2010) and worse performance on verbal comprehension and attention measures in children with low hematocrit (Steen et al., 2003).

Next, our study found that higher levels of creatinine were correlated with lower verbal skills and lower executive functioning scores. These relationships have not been investigated previously among individuals with SCD, to our knowledge. In other populations, researchers have speculated that higher levels of creatinine reflected subtle organ injury or overall higher disease burden. Indeed, among adults with chronic kidney disease, a similar inverse relationship between creatinine and cognitive functions has been reported (Elias et al., 2009; Khatri et al., 2009). In a longitudinal study of community-dwelling adults, increasing levels of creatinine were related to more rapid decline on a test of verbal learning and memory (Seliger, Wendell, Waldstein, Ferrucci, & Zonderman, 2015). Moreover, higher creatinine has been associated with worse scores on a mini-mental status exam, both in a sample of elderly Caucasian adults (Rajagopalan et al., 2013) and in patients undergoing cardiac rehabilitation (Caminiti et al., 2012).

Treatment implications

Understanding the cognitive functioning of symptomatic adults with SCD has implications for not only the patients and their families but also for the medical practitioners and members of multidisciplinary treatment teams. First, psychologists have a primary role in assessing and educating patients about their cognitive strengths and weaknesses. Assessment findings and recommendations should be reviewed with the patient and key family members and be explained using “real world” examples of how their strengths and weaknesses may manifest in their daily lives. For example, to minimize the clinical impact of slower processing speed, individuals should minimize distractions while working, take notes during meetings or medical appointments, and be prepared to ask people to repeat things or slow down during conversations. To ensure patients’ comprehension of their treatment regimen, providers should consider giving handouts or weblinks, avoid the use of overly technical language, and document known cognitive deficits in patients’ records to ensure helpful interactions with all members of the care team. Psychoeducational sessions or

a brief skills-based intervention to address cognitive weaknesses could be integrated into the patient's routine healthcare. These sessions also could incorporate information about obtaining appropriate educational or workplace accommodations. Additionally, brief cognitive screening should be implemented every 2 to 3 years, particularly in neurologically symptomatic patients, patients with symptoms of depression, or those with medication adherence concerns. This testing could have clinically significant implications for patients' overall treatment adherence, educational or occupational functioning, and early detection of cognitive declines. Finally, referrals should be made to vocational rehabilitation programs as slow processing speed can impact employment opportunities (Gelb, Shapiro, & Thornton, 2010; Strober, Chiaravalloti, Moore, & DeLuca, 2014). Individuals with SCD will benefit from the exploration of viable vocational alternatives, discussion of how their deficits may interfere with workplace functioning, and the provision of appropriate educational materials regarding federal and state legislation relevant to workplace accommodations.

Limitations and future directions

While this study is the first of its kind to examine symptomatic SCD patients' cognitive functioning compared with matched sibling controls, results should be considered in the context of several limitations. Most notably, our small sample size may have limited our ability to detect more significant differences between the patients and their siblings, and relationships among cognitive scores and laboratory variables among the patients. Therefore, replication with a larger sample of symptomatic adults with SCD is needed. In addition, while the lower processing speed in our sample of patients likely has had real-world implications throughout their lives, certain factors make it difficult to pinpoint fully the clinical significance of our findings. Specifically, many of the patients on our study had come to our center for a stem cell transplant and had not been working full-time due to the impact of their disease on their daily physical functioning. An investigation focusing on the impact of cognitive functioning on variables like occupational attainment, employment stability, and work trajectories would help elucidate further the picture of clinical significance.

Our data is limited to cognitive, PRO, and several medical and laboratory values. We were not able to include several other variables that have been proposed as correlates of cognitive outcomes in sickle cell disease, such as vascular pathology, cytokine levels, and neuroimaging variables (Andreotti et al., 2015; Jorgensen et al., 2016; Scantlebury et al., 2011). The research on these associations are nascent and an area for future investigation.

Finally, as mentioned previously, patients who come to the NIH for this time-intensive transplant study may be higher functioning than the general population of adults with symptomatic SCD, thus potentially narrowing the generalizability of the current study. Future studies should explore cognitive functioning to cytokine levels and neuroimaging variables among symptomatic adults with SCD. Further elucidation of the pathophysiology and the hematological processes in adults with SCD that relate to cognitive functioning may help to identify patients at highest risk for cognitive decline and to pinpoint targets for preventive interventions.

Conclusions

Our use of unaffected siblings with sickle cell trait as a comparison group represents a substantial improvement over prior studies, and allows us to isolate the impact of SCD on cognitive functioning more confidently. In our sample of symptomatic adults with SCD prior to planned matched sibling donor stem cell transplant, cognitive functioning is largely intact. Processing speed is an area of relative weakness compared to healthy siblings, which suggests that slowed processing is a result of SCD, although the precise mechanism remains unclear. Further, the relationship between pain intensity and self-reported executive functioning in our study points to the possibility that educational and employment limitations may stem from the interplay of these variables. Recognition of patients' clinically significant cognitive difficulties and effective implementation of the strategies outlined above by the patient and family members in cooperation with the multidisciplinary treatment team will likely improve overall care and quality of life in the SCD population.

Acknowledgements

The authors would like to thank the patients and their siblings who participated in this study. We also acknowledge the valuable assistance of Beth Link, RN, Wynona Coles, RN, Kate Roskom, RN, Kari Struemph, PhD, and Taryn Allen, PhD.

Financial support

This research was supported by the Intramural Research Program of the National Cancer Institute, National Institutes of Health. This project has been funded in whole or in part with federal funds from the National Cancer Institute, National Institutes of Health, under Contract No. HHSN261200800001E. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

REFERENCES

Adler LA, Faraone SV, Spencer TJ, Michelson D, Reimherr FW, Glatt SJ, … Biederman J (2008). The reliability and validity of self- and investigator ratings of ADHD in adults. Journal of Attention Disorders, 11(6), 711–719. [PubMed: 18025250]

Andreotti C, King AA, Macy E, Compas BE, & DeBaun MR (2015). The Association of Cytokine Levels With Cognitive Function in Children With Sickle Cell Disease and Normal MRI Studies of the Brain. Journal of Child Neurology, 30(10), 1349–1353. [PubMed: 25512362]

Baker KS, Gibson S, Georgiou-Karistianis N, Roth RM, & Giummarra MJ (2016). Everyday Executive Functioning in Chronic Pain: Specific Deficits in Working Memory and Emotion Control, Predicted by Mood, Medications, and Pain Interference. Clinical Journal of Pain, 32(8), 673–680.

Ballas SK (2010). Neurocognitive complications of sickle cell anemia in adults. JAMA, 303(18), 1862–1863. [PubMed: 20460628]

Berryman C, Stanton TR, Bowering KJ, Tabor A, McFarlane A, & Moseley GL (2014). Do people with chronic pain have impaired executive function? A meta-analytical review. Clinical Psychology Review, 34(7), 563–579. [PubMed: 25265056]

Bjekic J, Zivanovic M, Puric D, Oosterman JM, & Filipovic SR (2017). Pain and executive functions: a unique relationship between Stroop task and experimentally induced pain. Psychological Research.

Brown RT, Davis PC, Lambert R, Hsu L, Hopkins K, & Eckman J (2000). Neurocognitive functioning and magnetic resonance imaging in children with sickle cell disease. Journal of Pediatric Psychology, 25(7), 503–513. [PubMed: 11007807]

Caminiti G, Ranghi F, De Benedetti S, Battaglia D, Arisi A, Franchini A, … Volterrani M (2012). Cognitive impairment affects physical recovery of patients with heart failure undergoing intensive cardiac rehabilitation. Rehabilitation Research and Practice, 2012, 218928. [PubMed: 23326665]

Chapman JR, Norvell DC, Hermsmeyer JT, Bransford RJ, DeVine J, McGirt MJ, & Lee MJ (2011). Evaluating common outcomes for measuring treatment success for chronic low back pain. Spine (Phila Pa 1976), 36(21 Suppl), S54–68. [PubMed: 21952190]

Conners CK, Ehrhard D, & Sparrow D (1999). CAARS Adult ADHD Rating Scales. New York, NY: MHS.

Crawford RD, & Jonassaint CR (2016). Adults with sickle cell disease may perform cognitive tests as well as controls when processing speed is taken into account: a preliminary case-control study. Journal of Advanced Nursing, 72(6), 1409–1416. [PubMed: 26289301]

Dakwar E, Mahony A, Pavlicova M, Glass A, Brooks D, Mariani JJ, … Levin FR (2012). The utility of attention-deficit/hyperactivity disorder screening instruments in individuals seeking treatment for substance use disorders. Journal of Clinical Psychiatry, 73(11), e1372–1378.

Delis DC, Kaplan E, & Kramer JH (2001). Delis-Kaplan Executive Function System Examiner's Manual. San Antonio, TX: The Psychological Corporation.

Delis DC, Kramer JH, Kaplan E, & Ober BA (2000). California Verbal Learning Test - Second Edition. San Antonio, TX: Psychological Corporation.

Derogatis L (2000). Brief Symptom Inventory (BSI) 18: Administration, Scoring, and Procedures Manual. Minneapolis, MN: National Computer Systems.

Elias MF, Elias PK, Seliger SL, Narsipur SS, Dore GA, & Robbins MA (2009). Chronic kidney disease, creatinine and cognitive functioning. Nephrology Dialysis Transplantation, 24(8), 2446–2452.

Gelb SR, Shapiro RJ, & Thornton WJ (2010). Predicting medication adherence and employment status following kidney transplant: The relative utility of traditional and everyday cognitive approaches. Neuropsychology, 24(4), 514–526. [PubMed: 20604625]

Gold JI, Johnson CB, Treadwell MJ, Hans N, & Vichinsky E (2008). Detection and assessment of stroke in patients with sickle cell disease: neuropsychological functioning and magnetic resonance imaging. Pediatric Hematology Oncology, 25(5), 409–421. [PubMed: 18569843]

Helmstaedter C, Wietzke J, & Lutz MT (2009). Unique and shared validity of the "Wechsler logical memory test", the "California verbal learning test", and the "verbal learning and memory test" in patients with epilepsy. Epilepsy Research, 87(2-3), 203–212. [PubMed: 19782537]

Jefferson AL, Poppas A, Paul RH, & Cohen RA (2007). Systemic hypoperfusion is associated with executive dysfunction in geriatric cardiac patients. Neurobiology of Aging, 28(3), 477–483. [PubMed: 16469418]

Jorgensen DR, Rosano C, & Novelli EM (2016). Can neuroimaging markers of vascular pathology explain cognitive performance in adults with sickle cell anemia? A review of the literature. Hemoglobin, 40(6), 381–387. [PubMed: 27689914]

Kamada Y, Hashimoto R, Yamamori H, Yasuda Y, Takehara T, Fujita Y, … Miyoshi E (2016). Impact of plasma transaminase levels on the peripheral blood glutamate levels and memory functions in healthy subjects. BBA Clinical, 5, 101–107. [PubMed: 27051595]

Khatri M, Nickolas T, Moon YP, Paik MC, Rundek T, Elkind MS, … Wright CB (2009). CKD associates with cognitive decline. Journal of the American Society of Nephrology, 20(11), 2427–2432. [PubMed: 19729443]

King AA, Strouse JJ, Rodeghier MJ, Compas BE, Casella JF, McKinstry RC, … Debaun MR (2014). Parent education and biologic factors influence on cognition in sickle cell anemia. American Journal of Hematology, 89(2), 162–167. [PubMed: 24123128]

Kral MC, Brown RT, & Hynd GW (2001). Neuropsychological aspects of pediatric sickle cell disease. Neuropsychological Review, 11(4), 179–196.

Lanzkron S, Strouse JJ, Wilson R, Beach MC, Haywood C, Park H, … Segal JB (2008). Systematic review: Hydroxyurea for the treatment of adults with sickle cell disease. Annals of Internal Medicine, 148(12), 939–955. [PubMed: 18458272]

Laurence B, George D, & Woods D (2006). Association between elevated depressive symptoms and clinical disease severity in African-American adults with sickle cell disease. Journal of the National Medical Association, 98(3), 365–369. [PubMed: 16573300]

Mackin RS, Insel P, Truran D, Vichinsky EP, Neumayr LD, Armstrong FD, … Neuroimaging Adult Sickle Cell Anemia Study, G. (2014). Neuroimaging abnormalities in adults with sickle cell anemia: associations with cognition. Neurology, 82(10), 835–841. [PubMed: 24523480]

Melzack R (1987). The short-form McGill Pain Questionnaire. Pain, 30(2), 191–197. [PubMed: 3670870]

Murata S, Sawa R, Nakatsu N, Saito T, Sugimoto T, Nakamura R, … Ono R (2017). Association between chronic musculoskeletal pain and executive function in community-dwelling older adults. European Journal of Pain, 21(10), 1717–1722. [PubMed: 28722315]

Nunes S, Argollo N, Mota M, Vieira C, & Sena EP (2017). Comprehensive neuropsychological evaluation of children and adolescents with sickle cell anemia: a hospital-based sample. Revista Brasileira de Hematologia e Hemoterapia, 39(1), 32–39. [PubMed: 28270343]

Petkus AJ, Gum AM, Small B, Malcarne VL, Stein MB, & Wetherell JL (2010). Evaluation of the factor structure and psychometric properties of the Brief Symptom Inventory-18 with homebound older adults. International Journal of Geriatric Psychiatry, 25(6), 578–587. [PubMed: 20013879]

Pham UH, Andersson S, Toft M, Pripp AH, Konglund AE, Dietrichs E, … Solbakk AK (2015). Self-Reported Executive Functioning in Everyday Life in Parkinson's Disease after Three Months of Subthalamic Deep Brain Stimulation. Parkinsons Disease, 2015, 461453.

Puffer E, Schatz J, & Roberts CW (2007). The association of oral hydroxyurea therapy with improved cognitive functioning in sickle cell disease. Child Neuropsychology, 13(2), 142–154. [PubMed: 17364571]

Rajagopalan P, Refsum H, Hua X, Toga AW, Jack CR Jr., Weiner MW, … Alzheimer's Disease Neuroimaging, I. (2013). Mapping creatinine- and cystatin C-related white matter brain deficits in the elderly. Neurobiology of Aging, 34(4), 1221–1230. [PubMed: 23182131]

Roth RM, Isquith PK, & Gioia GA (2005). BRIEF-A: Behavioral Rating Inventory of Executive Function - Adult Version. Lutz, FL: Psychological Assessment Resources.

Sanger M, Jordan L, Pruthi S, Day M, Covert B, Merriweather B, … Kassim A (2016). Cognitive deficits are associated with unemployment in adults with sickle cell anemia. J Clinical and Experimental Neuropsychology, 38(6), 661–671.

Scantlebury N, Mabbott D, Janzen L, Rockel C, Widjaja E, Jones G, … Odame I (2011). White matter integrity and core cognitive function in children diagnosed with sickle cell disease. Journal of Pediatric Hematology Oncology, 33(3), 163–171.

Schatz J, Finke RL, Kellett JM, & Kramer JH (2002). Cognitive functioning in children with sickle cell disease: a meta-analysis. Journal of Pediatric Psychology, 27(8), 739–748. [PubMed: 12403864]

Scrimshaw SV, & Maher C (2001). Responsiveness of visual analogue and McGill pain scale measures. Journal of Manipulative Physiological Therapeutics, 24(8), 501–504. [PubMed: 11677548]

Seliger SL, Wendell CR, Waldstein SR, Ferrucci L, & Zonderman AB (2015). Renal function and long-term decline in cognitive function: the Baltimore Longitudinal Study of Aging. American Journal of Nephrology, 41(4-5), 305–312. [PubMed: 26201453]

Seo SW, Gottesman RF, Clark JM, Hernaez R, Chang Y, Kim C, … Lazo M (2016). Nonalcoholic fatty liver disease is associated with cognitive function in adults. Neurology, 86(12), 1136–1142. [PubMed: 26911638]

Steen RG, Emudianughe T, Hunte M, Glass J, Wu S, Xiong X, & Reddick WE (2005). Brain volume in pediatric patients with sickle cell disease: evidence of volumetric growth delay? American Journal of Neuroradiology, 26(3), 455–462. [PubMed: 15760849]

Steen RG, Miles MA, Helton KJ, Strawn S, Wang W, Xiong X, & Mulhern RK (2003). Cognitive impairment in children with hemoglobin SS sickle cell disease: relationship to MR imaging findings and hematocrit. American Journal of Neuroradiology, 24(3), 382–389. [PubMed: 12637286]

Stegen S, Stepanov I, Cookfair D, Schwartz E, Hojnacki D, Weinstock-Guttman B, & Benedict RH (2010). Validity of the California Verbal Learning Test-II in multiple sclerosis. Clinical Neuropsychology, 24(2), 189–202.

Strober L, Chiaravalloti N, Moore N, & DeLuca J (2014). Unemployment in multiple sclerosis (MS): utility of the MS Functional Composite and cognitive testing. Multiple Sclerosis, 20(1), 112–115. [PubMed: 23635909]

Strouse J (2016). Sickle cell disease. Handbook of Clinical Neurology, 138, 311–324. [PubMed: 27637966]

Vichinsky EP, Neumayr LD, Gold JI, Weiner MW, Rule RR, Truran D, … Neuroimaging Adult Sickle Cell Anemia Study, G. (2010). Neuropsychological dysfunction and neuroimaging abnormalities in neurologically intact adults with sickle cell anemia. JAMA, 303(18), 1823–1831. [PubMed: 20460621]

Wechsler D (1999). Wechsler Abbreviated Scale of Intelligence. San Antonio, TX: The Psychological Corporation.

Wechsler D (2008). Wechlser Adult Intelligence Scale - Fourth Edition. San Antonio, TX: NCS Pearson, Inc.

White DA, & DeBaun M (1998). Cognitive and behavioral function in children with sickle cell disease: a review and discussion of methodological issues. Journal of Pediatric Hematology Oncology, 20(5), 458–462.

Wiesner M, Chen V, Windle M, Elliott MN, Grunbaum JA, Kanouse DE, & Schuster MA (2010). Factor structure and psychometric properties of the Brief Symptom Inventory-18 in women: a MACS approach to testing for invariance across racial/ethnic groups. Psychological Assessment, 22(4), 912–922. [PubMed: 21133550]

Table 1.

Medical Diagnoses of the Patients ($N = 30$).

Medical Diagnosis	***n* (%)**
Overt stroke	2 (7)
Silent stroke	7 (23)
Transient ischemic attack	2 (7)
Hypertension	7 (23)
Pulmonary hypertension	5 (17)
Kidney disease	3 (10)
Liver disease	12 (40)
Iron overload (ferritin >1000 μg/L)	13 (43)
Avascular necrosis	11 (37)
Moya moya syndrome	0 (0)

Table 2.

Mean Values and Differences in Laboratory Variables for Patients and Siblings (n=27 patient-sibling pairs).

Laboratory Variable	Patients	Siblings		
	Mean (SD)	Mean (SD)	*t*	*p*
Creatinine	.69 (.41)	.88 (.16)	2.39	.024
Hemoglobin	8.8 (1.4)	17.4 (22.3)	2.12	.043
Fetal Hemoglobin	10.4 (7.0)	<1%	7.09	<.001
Alkaline Phosphotase	109.7 (65.4)	78.7 (23.7)	2.49	.019
ALT	42.7 (37.2)	43.4 (70.3)	0.04	.965
AST	43.2 (22.0)	27.2 (28.9)	2.21	.035
LDH	392.1 (151.7)	190.3 (57.5)	6.11	<.001

ALT = alanine aminotransferase. AST = aspartate aminotransferase. LDH = lactic acid dehydrogenase.

Table 3.

Mean Cognitive Scores of Patients and Siblings (N = 30 pairs).

Test / Index	Domain	Patients	Siblings		
		Mean (SD)	Mean (SD)	*t*	*p*
Performance IQ	Visual-spatial skills	103.4 (14.4)	102.2 (12.6)	.60	.55
Processing Speed Index	Processing Speed	91.0 (11.3)	100.6 (12.3)	−3.5	.002
Digit Span Backward	Working memory	10.9 (3.6)	10.7 (3.1)	.30	.77
DKEFS Trails Switching	Executive functioning	8.7 (3.2)	9.1 (3.2)	−.46	.65

DKEFS = Delis Kaplan Executive Function System.

Table 4.

Differences between Patients and Siblings on the BRIEF-A Self-report (N = 30 pairs).

BRIEF Subscale / Index	Patients	Siblings		
	Mean (SD)	Mean (SD)	*t*	*p*
Inhibit	51.0 (9.7)	44.5 (8.2)	2.6	.014
Shift	52.4 (11.9)	48.4 (9.3)	1.5	.14
Emotional Control	50.8 (10.9)	44.4 (8.4)	2.2	.04
Self-Monitor	47.8 (9.3)	42.6 (7.9)	2.0	.055
Initiate	57.1 (12.8)	48.0 (8.9)	3.0	.006
Working Memory	56.7 (12.5)	48.5 (8.8)	2.6	.014
Plan/Organize	51.2 (13.2)	46.4 (8.1)	2.3	.027
Task Monitor	51.5 (9.4)	48.1 (9.7)	1.2	.23
Organization of Materials	50.2 (11.4)	44.3 (7.2)	2.3	.028
Behavioral Regulation Index *	50.8 (10.5)	43.9 (8.6)	2.4	.02
Metacognition Index *	54.7 (11.6)	46.6 (8.9)	2.8	.009
Global Executive Composite	52.9 (11.3)	44.9 (9.2)	2.6	.015

BRIEF-A = Behavior Rating Index of Executive Functions, Adult Version.

* ANCOVA results controlling for effects of BSI-18 depression scores revealed no significant differences between the groups on the Behavioral Regulation Index or Metacognition Index.

Table 5.

Correlations between lab values and cognitive variables among patients.

	Creatinine	Alkaline Phosphatase	Hemoglobin	Fetal Hemoglobin
Performance IQ	−.13	.17	.23	−.23
Processing Speed Index	−.10	.25	.14	−.30
Digits Backward	−.15	−.11	.18	.10
DKEFS Trails Switching	−.45*	−.24	.05	−.25

* p<.05

** p<.01

DKEFS = Delis Kaplan Executive Function System.